# Adult-Onset Still's Disease Diagnosed During Pregnancy: Case Report

## *GEBELİKTE TANI ALAN YETİŞKİN TİP STİLL HASTALIĞI*

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## Abstract

Adult-onset rheumatoid arthritis diagnosed during pregnancy is very rare. Because it resembles several infectious, malignant and other rheumatological disorders, its diagnosis and treatment are often delayed. High-spiking fever with long duration during the organogenesis period exposes fetus to the well-known teratogen. A 28-year-old-woman with fever, eruptions, myalgia, arthralgia and fatigue applied at 6 weeks' gestation in her first pregnancy. After the challenging evaluation, she was diagnosed to have adult-onset Still's disease triggered by infectious mononucleosis. She was admitted on corticosteroid therapy that resulted in the remission of symptoms and a healthy live-born infant. Adult-onset Still's disease must be considered during the evaluation of the fever of unknown origin. The association between disease and pregnancy had not been described, however, in the present report we wanted to emphasize the teratogenity of maternal hyperthermia, which is the main symptom of the disease.

**Key Words:** Pregnancy, steroids, fever; teratogens, Still's disease, adult-onset

## Özet

Gebelikte tanı alan yetişkin başlangıçlı romatoid artrit çok nadirdir. Enfeksiyonları, malign hastalıkları ve diğer romatolojik hastalıkları taklit edebildiğinden tanı ve tedavide gecikilebilir. Organogenez sırasında ortaya çıkan uzun süreli yüksek ateş ise fetus için teratojendir. 28 yaşındaki kadın hasta ilk gebeliğinin 6. haftasında ateş, döküntüler, miyalji, artralji ve yorgunluk şikayetleriyle başvurdu. Yoğun araştırmalar sonucu hastaya enfeksiyöz mononükleozun tetiklediği yetişkin tip Still hastalığı tanısı kondu. Hastaya steroid tedavisi başlandıktan sonra semptomlar geriledi ve sağlıklı bir yenidoğan dünyaya getirdi. Sebebi bilinmeyen ateş etiyolojisinde yetişkin başlangıçlı Still hastalığı akılda tutulmalıdır. Hastalıkla gebelik arasındaki ilişki bugüne kadar tanımlanmamış olsa da biz bu yazıda hastalığın ana semptomu olan yüksek ateşin teratojen etkisini vurgulamak istedik.

**Anahtar Kelimeler:** Gebelik, steroidler, ateş, teratojenler, yetişkin başlangıçlı Still hastalığı

**Turkiye Klinikleri J Gynecol Obst 2007, 17:476-480**

Adult-onset Still's disease, is a rare systemic inflammatory disorder of unknown etiology and pathogenesis. Patients present with high fever accompanied by systemic manifestations such as arthralgia, fever, skin rash, lymphadenopathy and hepatosplenomegaly. It is a diagnosis of exclusion with nonspecific laboratory, imaging, pathology and immune-serology results. The differential diagnosis includes infectious diseases, especially viral exanthems, malignancies and other rheumatological diseases. The diagnosis is clinical and empirical, based on inclusion and exclusion criteria. There are at least 6 classifications;[1] Yamaguchi's criteria[2] (Table 1) appear to be the most sensitive (93.5%), followed by those of Calabro and Londino. Diagnosis of adult-onset Still's disease requires five or more criteria, including at least 2 major criteria.[3] There are no clear-cut diagnostic radiological or laboratory signs; the main symptoms and signs include arthralgia, fever, and eruption, enlargement of lymph nodes, liver, or spleen. Over 99% of patients with adult-onset Still's disease manifest with fever >39, 8ºC at some time during the course of their disease, and more than 94% will demonstrate the high spiking pattern.[3] Prominent acute-phase reaction and elevated leukocyte count is characteristic, being in

**Geliş Tarihi/*Received:*** 21.03.2007 **Kabul Tarihi/*Accepted:*** 01.05.2007

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**Table 1.** Diagnostic criteria of adult-onset Still's disease by Yamaguchi et al.

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| **Major criteria** |
| 1. Arthritis |
| (a) swelling or limitation of motion, warmth, pain, stiffness |
| (b) duration 6 weeks—one or more joints |
| (c) exclusion of other reason |
| 2. Fever: (39.8ºC or higher) persisting, intermittent |
| 3. Typical rash: persistent eruption is not characteristic of the disease |
| 4. Elevated leukocyte count (>10 000) |
| **Minor criteria** |
| 1. Sore throat |
| 2. Lymphadenopathy and/or spleen involvement (recent development of significant lymph node swelling, splenomegaly confirmed on palpitation or by echography) |
| 3. Elevated liver function tests (transaminases and/or lactate dehydrogenase)-not attributable to drug, toxicity or allergy |
| 4. Negative ANA and rheumatoid-factor tests |
| ***Five criteria are needed, at least two major*** |
| **Exclusion criteria** |
| 1. Infections, especially sepsis and infectious mononucleosis |
| 2. Malignancies, especially lymphomas |
| 3. Rheumatic diseases, especially polyarteritis nodosa and rheumatoid vasculitis |

strong correlation with the activity of the illness. The ferritinemia associated with adult-onset Still's disease is often seen in the active phase of the disease; however, the degree of elevation in the disease is disproportionate to the degree of inflammation.[4,5] The biological response to empirical steroid therapy adds meaningful information to the diagnosis. Immunoserology, by itself, will not help to set the diagnosis. Dermatological signs are rather unstable, appearing and disappearing quickly. Non-steroid anti-inflammatory drugs are usually not effective enough in cases with high fever; corticosteroids are needed. In order to reduce the minimal effective steroid dose, disease-modifying antirheumatic drug therapy is applied: mainly methotrexate or sulphasalazine.[6-10]

We hereby report adult-onset Still's disease manifested in the first trimester of the pregnancy. Symptoms led to multiple laboratory and imaging studies and delayed treatment, which exposed the fetus to maternal hyperthermia for a long time in the beginning of the pregnancy. In the literature, no definitive relationship between adult-onset Still's disease and pregnancy has been described and it has been suggested that adult-onset Still's disease can be associated with good maternal and fetal outcomes when treated appropriately. However, in the present report we wanted to stress gestational effects of maternal hyperthermia due to febrile illnesses like adult-onset Still's disease.

## Case Report

A 28-year-old nulliparous woman at 6 weeks' gestation was admitted with swelling and hyperemia on her right inferior palpebra, sore throat, fatigue, generalized myalgia and arthralgia, fever, diffuse eruptions and abdominal pain for 3 weeks. Before her admission, she was diagnosed as having tonsillitis and was given antibiotics. Sore throat with this non-exudative pharyngitis lasted few days and throat culture was negative. She was hospitalized with initial diagnosis of orbital cellulitis and she was started on intravenous ceftriaxone and ornidazole treatment. High-spiking pattern of the fever reaching a maximum of 40˚C with chills generally occurred in the afternoon and at night throughout her hospitalization. Eruption, with several millimeters in diameter appeared on the cheeks, chest, extremities, palms and soles, resembling urticaria. The diffuse non-pruritic rash frequently appeared during febrile attacks, and lasted for several hours following defervescence. Generalized myalgia and arthralgia severely limited her mobility. Lymphadenopathy manifested as generalized mild to moderate nodal enlargement of non-tender lymph nodes located in the cervical and axillary regions. Mild splenomegaly and diffuse abdominal pain accompanied by nausea were other clinical findings.

A comprehensive work-up for infectious, rheumatological and neoplastic etiologies were all negative. Infectious etiologies excluded upon serum and radiographic evaluations were brucellosis, leptospirosis, parvovirus, mycobacterial infection, cytomegalovirus, toxoplasma, rubella, hepatitis and human immunodeficiency virus. However, during the course of the disease elevation in the

titers of the Ebstein-Barr virus IgG accompanied to the Ebstein-Barr virus IgM positivity. Therefore, this finding has confirmed the recent infectious mononucleosis. Her throat, urine, sputum and blood cultures were all negative. Moreover, rheumatological markers including antinuclear antibody, rheumatoid factor, lupus anticoagulant and anticardiolipin antibodies were all non-directive.

Her laboratory evaluation revealed a hypochrome, microcytic anemia with a hemoglobin level of 8.5 g/dl and mild leukocytosis with WBC count 12500/mm³. Highly sensitive C-reactive protein was 7.30 mg/l with 140 mm/h erythrocyte sedimentation rate. Ferritinemia with a level of 263.64 ng/ml (4-204 normal value) was found. In the second week of her hospitalization, hepatic enzymes increased and alanine transaminase and aspartate transaminase were measured as 165 u/l and 178 u/l respectively. Levels of muscle enzymes were in the normal range however, electromyogram suggesting myositis yielded the skin and muscle biopsies. Non-spesific mild cutaneous vasculitis was reported as histopathological diagnosis therefore dermatomyositis was excluded. There were no abnormal findings in her echocardiography. Abdominal ultrasonography was normal except mild splenomegaly. Lymph node biopsy excluded lymphoproliferative diseases. Second trimester screening revealed AFP: 0.97 MoM and lessened neural tube defect risk.

The fetus had normal anatomic survey results and its size was appropriate for gestational age. Serial sonography was performed for fetal growth. At 17 weeks, we performed amniocentesis for evaluation of fetal infection. PCR examinations of the amniotic fluid for several infectious agents were negative. They included HCV, HBV, HSV1, HSV2, CMV, *Toxoplasma gondii*, Parvovirus B19, *Brucella*, *Chlamidia-Neisseria* and EBV. Analysis of the amniotic fluid revealed CRP: 0.92 (0-6 mg/l) C3: 4.3 (88-201 mg/dl) C4: 1.4 (16-47 mg/dl) IL-1 alpha <5.0 ng/l.

After the exclusion of infectious, malignant and inflammatory causes, a diagnosis of adult-onset Still's disease meeting the Yamaguchi criteria was made and she was started on 16 mg of oral prednisone daily. The patient experienced immediate improvement with resolution of fever, rash and arthralgias and she was discharged from the hospital after 2 weeks. The prednisone was gradually decreased and eventually discontinued at 36 weeks' gestation. Within the 32nd gestational week the patient experienced the mild flares of Still's disease consisting of arthralgias and rash without fever. The patient did not have recurrent flares of disease during the remainder of her pregnancy or post-partum period.

The patient had an elective cesarean section at 39th gestational week and delivered a healthy female infant weighing 3570 grams, with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively.

## Discussion

Adult-onset Still's disease is a heterogeneous pathological entity with a range of etiologies, manifestations and prognosis. It was first described in children by Still in 1897 and in adults by Bywaters in 1971.[11] In 1980, Stein et al.[12] reported the first case of adult-onset Still's disease in pregnancy which was followed by only a few reports in pregnancy.[13] It remains a difficult clinical diagnosis, largely because of its rarity, variable manifestations and a lack of diagnostic tests or pathognomonic features.[14] The patient in our case applied with swelling and hyperemia on her right inferior palpebra, sore throat, fatigue, generalized myalgia and arthralgia, fever, diffuse eruptions and abdominal pain for three weeks.

Etiology of the illness is not fully understood; the emphasis is on its genetic versus environmental origin. In the pathogenesis of the disease, systemic vasculitis should also be considered. Infectious agents that have also been implicated in triggering the onset or recurrence of the disease include; rubella, Epstein-Barr virus, mumps, adenovirus, cytomegalovirus, parvovirus, mycoplasma, echovirus, and *Yersinia enterocolitica*.[3] A positive serological reaction to some viruses or bacteria can be demonstrated in 48% of cases.[14] Cush concludes that adult-onset Still's disease is a cytokine-driven disorder, with the curious diurnal variation in fever and other systemic features suggesting an underlying circadian rhythm.[14]

In the present report, serologically confirmed recent EBV infection (EBV IgM positivity with rising titers of EBV IgG) suggests enfectious mononucleosis as a trigger to the disease. Only the role of stress has been proven as a risk factor of the disease; there is no correlation with smoking, alcohol drinking, vaccination, transfusion, surgical intervention, pregnancy or previous diet. No connection has been shown with tonsillectomy, adenoidectomy, appendectomy, asthma, rhinitis allergica or dust inhalation.[15] No such possible etiological factor other than EBV infection was present in our patient.

Before admission, patients are generally examined with the diagnosis of fever of unknown origin and undergo work-up. They have been given a number of antimicrobial agents (in most of the cases empirically), so the possibility of having an infection can be almost completely excluded. If the reason for fever of unknown origin is not uncovered within 3 weeks, it is rarely of infectious origin.

In the literature, no definitive relationship between adult-onset Still's disease and pregnancy has been described and it has been suggested that adult-onset Still's disease can be associated with good maternal and fetal outcomes when treated appropriately.[16-18] Patients are usually subject to multiple diagnostic procedures and laboratory tests as well as empiric treatment with antibiotics and other medications. As a result, diagnosis and treatments are often delayed. This condition may not be important on the course of the disease and the patient. Nevertheless, we want to emphasize the impact of the delayed treatment on the fetus.

Nowadays, we know the teratogenic effects of hyperthermia in men and experimental animals.[19,20,21] Fever was found to be a teratogen initially in animals. Subsequently, it was found to be a cause for concern in humans when similar patterns of defects were observed.[22] Fever was found to be a cause especially for neural tube defects, such as spina bifida, anencephaly and encephalocele.[22] Hyperthermia is a physical agent with a dose-response curve for abortions and malformations but these effects can be lessened in some circumstances by the heat shock response.[23,24]

The nature of the specific associated anomalies appears to relate to the extent, duration, and timing of maternal fever.[25] Neural tube defects including spina bifida, anencephaly and encephalocele are the most common fetal anomalies caused by fever and targeted ultrasonography for these specific anomalies during follow-up is required for pregnancies complicated by fever, especially during organogenesis. Therefore, in adult-onset Still's disease during pregnancy we have to consider the effects of human hyperthermia teratogenesis. In the present case, the fetus was exposed to maternal hyperthermia, approximately for five weeks including the organogenesis period. The patient was provided with the information of possible deleterious effects of hyperthermia on the fetus. Once the informed consent was provided, careful follow-up of the pregnancy revealed no detected abnormalities and the pregnancy ended up with a healthy newborn. As a result, a pregnancy that is complicated with adult-onset Still's disease should be considered as a high-risk pregnancy, particularly if the disease covers the first trimester.

## REFERENCES

1. Masson C, Le Loet X, Liote F, et al. Comparative study of 6 types of criteria in adult Still's disease. J Rheumatol 1996;23:495-7.
2. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheum 1992;19:424-30.
3. Wouters JM, Van do Putte LB. Adult-onset Still's disease: Clinical and laboratory features, treatment and progress of 45 cases. QJ Med 1986;235:1055-65.
4. Kelly J, Chowienczyk P, Gibson T. Sore throat and hyperferritinemia. JR Soc Med 2001;94:400-1.
5. Fautrel B, Le Moel G, Saint-Marcoux B, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol 2001;28:322-9.
6. Fautrel B, Borget C, Rozenberg S, et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. J Rheumatol 1999;26:373-8.
7. Jung JH, Jun JB, Yoo DH, et al. High toxicity of sulfasalazine in adult-onset Still's disease. Clin Exp Rheumatol 2000;18:245-8.
8. Vignes S, Wechsler B, Amoura Z, et al. Intravenous immunoglobulin in adult Still's disease refractory to nonsteroidal anti-inflammatory drugs. Clin Exp Rheumatol 1998;16:295-8.
9. Marchesoni A, Ceravolo GP, Battafarano N, Rosetti, A, Tasi S, Fantini F. Cyclosporin A in the treatment of adult onset Still's disease. J Rheum 1997;24:1582-7.

10. Fleischmann R, Iqbal I, Nandeshwar P, Guiceno A. Safety and efficacy of disease-modifying anti-rheumatic agents: Focus on the benefits and risks of etanercept. Drug Saf 2002;25:173-97.
11. Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30:121-33.
12. Stein GH, Cantor B, Panush RS. Adult Still's disease associated with pregnancy. Arthritis Rheum 1980;23:248-50.
13. Pan VL, Haruyama AZ, Guberman C, Kitridou RC, Wing DA. Newly diagnosed Adult-onset Still's disease in pregnancy. Obstet & gynecol 2003;101:1112-6.
14. Cush JJ. Adult-onset Still's disease. Bull Rheum Dis 2000; 49:1-4.
15. Sampalis JS, Medsger Jr TA, Fries JF, et al. Risk factors for adult Still's disease. J Rheum 1996;23:2049-54.
16. Sampalis JS, Esdaile JM, Medsger TA. A controlled study of the long-term prognosis of adult Still's disease. Am J Med 1995;98:384-8.
17. Le Loet X, Dragon A, Duval C, Thomine E, Lauret P, Humbert G. Adult-onset Still's disease and pregnancy. J Rheumatol 1993;20:1158-61.
18. De Miguel E, Custa M, Martin-Mola E, Gijon-Banos J. Adult Still's disease and pregnancy. J Rheumatol 1992;19:498.
19. Peterka M, Peterkova R, Likovsky Z. Teratogenic and lethal effects of long-term hyperthermia and hypothermia in the chick embryo. Reprod Toxicol 1996;10:327-32.
20. Edwards MJ. Congenital defects in guinea pigs: Fetal resorptions, abortions, and malformations following induced hyperthermia during early gestation. Teratology 1969;2:313-28.
21. Germain MA, Webster WS, Edwards MJ. Hyperthermia as a teratogen: parameters determining hyperthermia-induced head defects in the rat. Teratology 1985;31:265-72.
22. Lynberg MC, Khoury MJ, Lu X, Cocian T. Maternal flu, fever, and the risk of neural tube defects: A population-based case-control study. Am J Epidemiol 1994;140:244-55.
23. Kline J, Stein Z, Susser M, Warburton D. Fever during pregnancy and spontaneous abortion. Am J Epidemiol 1985;121:832-42.
24. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Maternal fever and birth outcome: A prospective study. Teratology 1998;58:251-7.
25. Graham JM Jr, Edwards MJ, Edwards MJ. Teratogen update: Gestational effects of maternal hyperthermia due to febrile illnesses and resultant patterns of defects in humans. Teratology 1998;58:209-21.